

The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SAUL TZIPORI,
RAMASWAMY BALAKRISHNAN, and ARTHUR DONOHUE-ROLFE

Appeal 2006-2945¹
Application 10/041,958
Technology Center 1600

Decided: August 21, 2007

Before DONALD E. ADAMS, LORA M. GREEN, and NANCY J. LINCK,
Administrative Patent Judges.

ADAMS, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 26-36, the only
claims pending in this application. We have jurisdiction under 35 U.S.C.
§ 6(b).

¹ Heard August 8, 2007.

INTRODUCTION

The claims are directed to a dosage formulation. Claims 26, 28, 30, 31, and 32 are illustrative:

26. A dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II *in vivo*, wherein the antibodies are specifically reactive with a single subunit of the Shiga like toxin II produced by *Escherichia coli* which causes hemolytic uremic syndrome, to prevent or treat hemolytic uremic syndrome in a human.

28. The dosage formulation of claim 26, wherein the antibodies are produced by recombinant DNA methodology.

30. The dosage formulation of claim 26, wherein the antibodies bind to the alpha subunit of the Shiga like toxin II.

31. The dosage formulation of claim 26 wherein the antibodies are effective to prevent neurological signs of hemolytic uremic syndrome or lesions, wherein the neurological signs or lesions are selected from the group consisting of bloody diarrhea, acute renal failure, cerebral hemorrhaging, bacterial shedding into feces, bacterial lesions, paddling, head-pressing, ataxia, convulsions and wasting.

32. The dosage formulation of claim 26, wherein the antibodies are effective to prolong survival.

The Examiner relies on the following prior art references to show unpatentability:

Queen	WO 90/07861	Jul. 26, 1990
Krivan	US 5,512,282	Apr. 30, 1996
Williams	US 6,080,400	Jun. 27, 2000

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Perera, *Isolation and Characterization of Monoclonal Antibodies to Shiga-Like Toxin II of Enterohemorrhagic Escherichia coli and Use of the Monoclonal Antibodies in a Colony Enzyme-Linked Immunosorbent Assay*, 26(10) J. Clinical Microbiology 2127-2131 (1988)

Engleman et al. (Engleman), *Human lymphoblastoid Cell Lines as Fusion Partners, in Human Hybridomas and Monoclonal Antibodies*, pp. 23-27 (Edgar G. Engleman et al., eds., Plenum Press, New York 1985)

The rejection as presented by the Examiner is as follows:

Claims 26-36 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engleman.

We affirm.

DISCUSSION

According to Appellants, “[t]here is a related appeal [(Appeal No. 2005-1921)] in Serial No: 10/230,614 filed August 29, 2002, which directly affects . . . or which may have a bearing on the Board’s decision in this appeal” (Br. 2). As Appellants point out, a Decision was entered in Appeal No. 2005-1921 on September 26, 2005 affirming the rejection of claim 1 under 35 U.S.C. § 103, as being unpatentable over the combination of Krivan, MacLeod, Queen and Engleman (Decision 9). All claims on appeal in Appeal No. 2005-1921 fell together with claim 1 (*id.*). For clarity, we reproduce claim 1 of Appeal No. 2005-1921:

1. A method to prevent or treat hemolytic uremic syndrome in a human individual exposed to or infected by *Escherichia coli* producing Shiga-like toxin II, comprising:
administering intradermally, subcutaneously, intravenously, or intramuscularly, to an individual presenting with bloody diarrhea, diagnosed with infection by

Escherichia coli producing Shiga-like toxin II, or exposed to an individual infected with or exposed to the same source of infection with *Escherichia coli* producing Shiga-like toxin II an effective amount of monoclonal human or humanized antibodies consisting of antibodies neutralizing Shiga like toxin II, to prevent or treat hemolytic uremic syndrome.

While the subject matter in Appeal No. 2005-1921 was drawn to a method and the subject matter before us on this Appeal is drawn to a composition, a number of the evidentiary references relied upon by the Examiner are the same. Nevertheless, while Appellants recognize that the Decision in Appeal No. 2005-1921 would likely affect or have a bearing on this Appeal, Appellants make no attempt to distinguish the evidentiary findings and conclusions of law in Appeal No. 2005-1921 from the evidence of record in this Appeal.

Claims 26-36 stand rejected 35 U.S.C. § 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman. The Examiner makes the following findings of fact:

Krivan:

1. Teaches “purified high titer, monospecific polyclonal antibodies to Shiga-like toxin . . .” (Answer 3).
2. Obtained the monospecific polyclonal antibodies by inoculating a bovine animal with a purified active *E. coli* derived Shiga-like toxin (SLT), “selected from the group consisting of SLT I, SLT II, SLT IIV and mixtures thereof” (*id.*).

3. Teaches “passive immunization of a human or animal against SLT toxinemia comprising administering to the human or animal a prophylactically effective amount of the elicited antibody” (Answer 3-4).
4. Teaches “that SLT toxinemia can lead to hemolytic uremic syndrome” (Answer 4).
5. Teaches that their “invention provides an antitoxin to one or more SLTs” (*id.*).
6. Teaches “that ‘[a] single type of SLT, such as SLT-II or a variant thereof, such as SLT-IIvp can be injected [and that] [t]his provides polyclonal antibodies that are monospecific to just that type of SLT or variant” (*id.*).

Perera:

7. Teaches “five monoclonal antibodies which bind to the α -subunit of SLT-II and were able to neutralize the toxin” (*id.*).

Williams:

8. Teaches that “[s]tudies of Shiga toxin B subunit suggest that neutralizing epitopes may also be present at both the N- and C-terminal regions of VT1 and VT-2 B subunits [and that] [p]olyclonal antibodies raised against peptides from these regions . . . show partial neutralization of Shiga toxin . . .” (*id.*).
9. Teaches that “VT1 and VT2 correspond to SLT-1 and SLT-II” (*id.*).

The combination of Krivan, Perera, and Williams:

10. Does not teach monoclonal human or humanized antibodies (*id.*).

Queen:

11. Teaches “methodology for the production of CDR-grafted antibodies having CDRs derived from the variable regions of non-human antibodies and framework regions derived from human antibodies . . .” (Answer 5).

12. Teaches that “CDR-grafted antibodies were recognized to be useful reagents for diagnostic and therapeutic applications” (*id.*).

13. Teaches “that humanized antibodies are substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin” (*id.*).

Engelman:

14. Teaches “that methods for constructing human-human hybrids that secrete human monoclonal antibodies . . . were well known in the art at the time of Applicants['] invention” (*id.*).

Based on the foregoing factual findings, the Examiner concludes that “it would have been prima facie obvious to one of ordinary skill in the art to have generated a humanized antibody or a human monoclonal antibody as taught by Queen . . . and Engelman [respectively] . . ., for use in the method disclosed by Krivan . . .” (Answer 5-6). We find no error in the Examiner’s reasoning and conclusion.

In further view of the foregoing factual findings, the Examiner concludes that it would have been obvious to a person of ordinary skill in the

art at the time of Appellants' claimed invention to modify the combination of Krivan, Queen and Engelman to utilize an anti-SLT II α subunit antibody or an anti-SLT II β subunit antibody in view of the respective teachings of Perera and Williams of neutralizing monoclonal antibodies against these specific subunits (Answer 6). Again, we find no error in the Examiner's reasoning and conclusion.

We also find that the evidence of record supports the Examiner's conclusion that a person of ordinary skill in the art at the time the invention was made would have been motivated to produce a humanized antibody or human monoclonal antibody "based on the advantages described by Queen . . . and Engelman . . . (i.e., substantially decreased immunogenicity)" (*id.*).

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993), *citation omitted*. We conclude that the Examiner has met his burden of establishing a *prima facie* case of obviousness. Accordingly, the burden of coming forward with evidence or argument was properly shifted to Appellants.

Appellants separately argue the claims as they relate to the following four claim groupings: (I) claims 27-29; (II) claims 30 and 33; (III) claim 31; and (IV) claims 32 and 34-36 (Br. 4-5; Br. 29-30). The claims within each grouping that contains multiple claims will stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii) (2006). Further, notwithstanding Appellants' failure to address the only independent claim on Appeal (claim 26) in their claim

grouping, we will treat claim 26 as standing or falling alone. Accordingly, we limit our discussion to representative claims 26, 28, 30, 31, and 32.

Claim 26:

Claim 26 is drawn to a dosage formulation. We interpret the term “dosage formulation” to be a pharmaceutical composition. According to Appellants’ Specification,

[t]he pharmaceutical compositions are prepared by methods known to one of skill in the art. In general, a monoclonal antibody, a cocktail of monoclonal antibodies or monospecific polyclonal antibodies are admixed with a carrier and other diluents necessary to prepare the pharmaceutical composition, so that it is in a stable and administrable form.

(Specification 10.) The claimed formulation comprising an effective amount of human or humanized monoclonal antibodies to prevent or treat hemolytic uremic syndrome (HUS) in a human. Claim 26 requires that the antibodies have two properties:

- (1) they consist of antibodies that neutralize SLT II *in vivo*; and
- (2) they are specifically reactive with a single subunit of the SLT II produced by *Escherichia coli* which causes HUS.

The Examiner’s factual findings and conclusion of obviousness based on these facts are set forth above. In response, Appellants make a number of assertions as outlined below. We take each of Appellants’ assertions in turn.

Appellants assert that:

Krivan:

A1. “Krivan does not place one of skill in the art with antibodies to Stx2 [(Shiga like toxin II)] which would be effective to treat or prevent human uremic syndrome” (Br.² 14, emphasis removed).

We disagree, and direct Appellants’ attention to, for example, claim 1 of Krivan, which reads on purified IgG monospecific polyclonal antibodies to each of SLT I, SLT II, and SLTIIv *individually* and as a mixture. Krivan teaches that an “object[ive] of the invention is to provide pharmaceutical compositions for the prevention, amelioration, or treatment of disease in a human or animal caused by an SLT together with methods of using such compositions” (Krivan, col. 6, ll. 3-6). As the Examiner points out, Krivan’s pharmaceutical compositions comprise “purified high titer, monospecific polyclonal antibodies to Shiga-like toxin . . .” (Findings of Fact (FF) 1; Answer 3). In addition, we direct attention to Krivan’s claim 17 which is directed to a method for passive immunization of a human or animal against SLT toxemia comprising administering a prophylactically effective amount of the antibody of claim 1 and claim 18 which is directed to a method for the treatment of SLT toxemia in a human or animal comprising administering a therapeutically effective amount of the antibody of claim 1. Further, Krivan teaches that SLT toxemia is associated with a spectrum of diseases including HUS (Krivan, col. 1, ll. 46-49). Therefore, we find that Krivan teaches that HUS can be treated or prevented, in a human, by passive immunization of a

² All reference to Appellants’ Brief (Br.) are to the Substitute Appeal Brief received March 29, 2006.

purified IgG monospecific polyclonal antibodies to SLT II. Accordingly, we are not persuaded by Appellants' assertion to the contrary.

A2. Krivan appears to describe only those "SLT forms that cause animal disease, not . . . the Stx2 form causing HUS" (*id.*).

This assertion is inconsistent with Krivan's disclosure. Specifically, Krivan discloses that "[t]he invention . . . comprises methods and pharmaceutical compositions for the prevention, amelioration, or treatment of disease in a human or animal caused by an SLT or by bacteria that produce an SLT" (Krivan, col. 6, ll. 37-44). As discussed above, Krivan teaches that HUS is one such disease caused by an SLT or by bacteria that produce an SLT. Accordingly, we do not find Appellants' assertion persuasive.

A3. Krivan does not recognize that different *E. coli* strains infect different hosts. Therefore, one cannot extrapolate from reagents in one species, *e.g.*, cattle, for use in another, *e.g.*, humans, "since there are differences in the toxins, and in the host species, [therefore,] cattle and humans which are infected differently have different diseases" (Br. 15).

It is unclear why Appellants' attempt to distinguish Krivan by focusing of the differences between cattle and humans. Krivan recognizes that cattle respond to SLTs differently than humans and other animals, and for that reason selected cattle as the animal of choice for producing antibodies against SLTs. *See* Krivan, col. 5, ll. 42-53; col. 8, ll. 16-35. Further, contrary to Appellants' assertion, no extrapolation is necessary on

this record because Krivan expressly teaches the treatment of humans. Accordingly, we are not persuaded by this assertion.

A4. “There is no disclosure or suggestion [in Krivan] . . . to obtain a human monoclonal antibody that will bind to, and specifically neutralize, Stx2 from the *E. coli* in humans” (*id.*).

For the reasons set forth above, we disagree with this assertion.

A5. “Krivan does not . . . recognize that the bacteria that infect cattle are unable to infect humans and cause HUS. Therefore, Krivan does not disclose nor enable treatment of humans to prevent HUS” (*id.*).

For the reasons set forth above, we disagree with this assertion.

A6. Krivan states that “his antibodies and invention are not, and cannot be, useful in humans.” (*id.*).

For the reasons set forth above, this assertion is directly refuted by Krivan’s disclosure. Accordingly, we do not find it persuasive.

A7. The Krivan “patent makes clear, the animals to be treated to make antibodies do not possess receptors for the toxin (thereby excluding humans), and the resulting antibodies therefore would not be administerable to humans (it is well known one cannot administer bovine antibodies by injection to humans)” (*id.*, emphasis removed).

This assertion lays the foundation for all of Appellants’ assertions and is based on a misinterpretation of Krivan’s disclosure. Animals, e.g. cattle (Krivan, col. 8, l. 31) as compared to other mammals or humans (Krivan,

col. 8, ll. 16-19), whose cells only contain low levels of receptors for SLTs (Krivan, col. 8, ll. 25-26) *are not being treated* – they are being used to produce antibodies that are to be used for passive immunization (Krivan, col. 8, ll. 31-35), e.g., the treatment of other animals, including humans. Accordingly, we are not persuaded by Appellants' assertion.

A8. "Krivan teaches away from treating humans by stating that the method is for the treatment of animals that have few or no receptors to SLTs. Humans have receptors. That is why cattle and humans are different" (Br. 17).

For the foregoing reasons, we disagree with Appellants' assertion.

Perera:

A9. "Perera does not teach antibodies for therapeutic use and suggests that antibodies to subunits of Stx2 are not as effective as antibodies to Stx1" (Br. 14).

Appellants are correct in their assertion that Perera does not teach the therapeutic use of their antibodies. Perera does, however, teach five monoclonal antibodies that bind the α -subunit of SLT-II (Perera, page 2130, col. 1, ll. 34-35) and are capable of neutralizing the cytotoxicity of SLT-II (Perera abstract). As the Examiner explains, "[n]eutralizing antibodies, by definition, neutralize the effect of the toxin, consequently motivation to specifically incorporate antibodies with this property would be readily apparent to one of ordinary skill in the art" (Answer 8). We find no error in the Examiner's assertion.

Further, when Perera is considered in the context of the combination of prior art relied upon by the Examiner, we find that a person of ordinary skill in the art would have understood that Perera's antibodies, which are capable of neutralizing the toxicity of the SLT II toxin, would be useful in the method taught by Krivan, as would human or humanized variants of Perera's antibodies.

Accordingly, we are not persuaded by Appellants' intimation that simply because Perera does not teach a therapeutic use for his antibodies, a person of ordinary skill in the art would not understand Perera's contribution to the combination of references relied upon. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007). *See also id.* At 1742, 82 USPQ2d 1397 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

Further, while Appellants assert that Perera "suggests that antibodies to subunits of Stx2 are not as effective as antibodies to Stx1," they fail to explain what they intend by "effective" or identify the specific portion of Perera that supports this assertion. Accordingly, it is unclear if Appellants' assertion is based on a correct or fair reading of Perera. Nevertheless, because Appellants do not direct attention to any particular portion of Perera which supports their assertion, we are unable to evaluate Appellants' assertion in the context of Perera's teaching. In the absence of a contextual basis in Perera to evaluate Appellants' assertion, we do not find it persuasive.

A10. Perera makes “no mention of therapy other than to note that the [S]higa like toxins may play a role in disease ‘although no direct proof for the involvement of SLTs in pathogenesis has yet been demonstrated’” (Br. 18-19; Reply Br. 8).

We agree that Perera makes no mention of therapy, and recognizes that SLTs’ involvement in disease was unknown as of the 1988 publication date of the reference (Perera, page 2130, col. 2, ll. 21-25). We are, however, not persuaded that Perera’s acknowledgement of the state of the art in 1988 has any effect on the combination of references as relied upon by the Examiner which in combination teach the use of human or humanized antibodies to SLT II, SLT II α -subunit, or β -SLT II subunit for the treatment of HUS in a human.

A11. Perera teaches “that none of the antibodies reactive only with Stx2 could be used to detect organisms; antibodies to Stx2 which were effective were only able to be used to detect organisms producing both Stx1 and Stx2. Accordingly, one would not be led by Perera to use these antibodies in therapy, nor one would [sic] have a reasonable expectation of success using just an antibody to Stx2, much less to a single subunit of Stx2” (Br. 19).

There is no requirement in claim 26 that the antibodies detect an organism. Accordingly, we are not persuaded by Appellants’ assertion.

Further Appellants’ assertion appears to be based on a misinterpretation of Perera. According to Perera, the “*E. coli* strains used in this study included clinical isolates from humans with diarrhea, hemorrhagic colitis, or hemolytic-uremic syndrome, calves with diarrhea, and pigs with edema disease. . .” (Perera, page 2127, col. 2, ll. 5-8). Of the 10 SLT II

strains 7 were reactive with monoclonal antibody 11E10 and 6 were reactive with monoclonal antibody 2E1 (Perera, page 2130, Table 2). Of these 10 strains, only 3 strains did not react in a colony ELISA with any of the neutralizing MAbs to SLT-II (Perera, page 2131, ll. 11-13). According to Perera, “[t]hese three strains may produce SLTs more like the SLT-IIv of pig edema disease strains. In support of this possibility is the observation that none of the nine SLT-IIv-producing edema disease strains were detected by the MAbs to SLT-II in colony ELISA” (Perera, page 2131, col. 1, ll. 17-20). Therefore, contrary to Appellants’ intimation, 70% of the SLT-II strains tested reacted with Perera’s neutralizing MAbs. According to Perera, “[a]ll the neutralizing MAbs generated in the present study recognized the A subunit of SLT-II” (Perera, page 2130, col. 1, ll. 34-35). Therefore, we are not persuaded by Appellants’ assertion that a person of ordinary skill in the art “would not be led by Perera to use these antibodies in therapy, nor one would [sic] have a reasonable expectation of success using just an antibody to Stx2, much less to a single subunit of Stx2” (Br. 19). To the contrary, we find that Perera’s teaching that 70% of the SLT-II strains tested reacted with Perera’s neutralizing MAbs provides more than a reasonable expectation of success in using a neutralizing MAb as a therapeutic agent in a dosage formulation for the treatment or prevention of hemolytic uremic syndrome in a human when taken in view of the combination of reference relied upon by the Examiner. For obviousness under §103, all that is required is a reasonable expectation of success. *In re O’Farrell*, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). In our opinion, when taken in the context of the prior art relied upon, Perera provides a reasonable expectation that a formulation comprising antibodies to SLT II α -subunit would be

effective in treating HUS. Accordingly, we do not find Appellants' argument persuasive.

Williams:

A12. "It is not clear that Williams is available as prior art, even under 35 U.S.C. [§] 102(e), since it issued on an application filed March 13, 1997, well after [A]ppellants' priority date of November 15, 1996" (Br. 17).

"To fully demonstrate [that] the teachings of Williams are entitled to the filing date of the CIP application, [the Examiner enclosed] page 9 of the CIP Application, 08/410,058" with the Answer (Answer 9). According to the Examiner "[t]his page demonstrates verbatim support of the text relied upon in the rejection" (*id.*). While, Appellants address Williams in their Reply Brief, they do not refute the Examiner's assertion that Williams is properly available as prior art (*see, e.g.*, Reply Br. 6-7). Accordingly, we do not find this argument persuasive.

A13. "Williams is drawn to the use of avian antibodies elicited by immunization of birds with recombinant, preferably cross-linked toxin fragments. . . . There is no teaching or even recognition that one cannot inject avian antibodies into humans . . ." (Br. 17-18, emphasis removed).

Appellants' argument is not consistent with the combination of evidence relied upon by the Examiner. For example, Williams expressly states that the "antitoxins are useful in the treatment of humans and other animals intoxicated with at least one bacterial toxin" (Williams, abstract). Further, notwithstanding Williams' express teaching of the treatment of humans, the combination of evidence relied upon by the Examiner teaches

that a person of ordinary skill in the art would have been motivated to use human or humanized (e.g., recombinant) antibodies in a dosage formulation intended for the treatment of humans (*see, e.g.*, Queen and Engleman). Accordingly, we are not persuaded by Appellants argument.

A14. “[B]ased on example 19 of Williams, the mere fact that an antibody is a neutralizing antibody (i.e., able to complex with antigen and neutralize charge so that a precipitate is formed) does not mean it will be therapeutically effective” (Br. 19; *see also* Br. 18).

Appellants’ assertion is simply a conclusion. Appellants do nothing to favor this record with an explanation of the factual basis that supports this conclusion. In this regard, we find it unclear as to why Appellants focus on Example 19 of the 20 examples set forth in Williams and base their assertion solely on this example. In this regard, we note that in Example 16 Williams reports that “VT2B-Q IgY was capable of preventing lethality by rVT2 [(recombinant SLT II)]” (Williams, col. 62, ll. 37-39). Curiously, this specific antibody was not tested in Example 19. Further, Appellants’ assertion appears to contradict the express teachings in Williams, specifically that “[t]he present invention relates to antitoxin therapy for humans and other animals” (Williams, col. 16, ll. 62-63). Simply stated, without an explanation of the factual basis supporting this assertion, we find Appellants’ assertion unpersuasive. It is well settled that arguments of counsel cannot take the place of evidence lacking in the record. *Estee Lauder Inc. v. L’Oreal, S.A.*, 129 F.3d 588, 595, 44 USPQ2d 1610, 1615 (Fed. Cir. 1997).

A15. Williams' "results would not be predictive of efficacy in humans" (Br. 18).

Again, Appellants fail to set forth a factual foundation to support this conjecture.

Queen:

A16. Queen's "techniques do not incorporate the use of an intact 'immune system' to produce . . . humanized monoclonal antibodies" (Br. 19).

While this may be true, Appellants' point is less than clear. As one of ordinary skill in this art would appreciate, an intact immune system is not necessary to produce recombinant antibodies according to Queen's method. While Appellants' claim 26 requires "human or humanized antibodies," no claim presented for our review requires "an intact immune system to produce humanized monoclonal antibodies." Queen teaches the production of humanized antibodies. Queen taken together with Krivan, alone or in combination with Perera and Williams, teaches a humanized SLT-II antibody. Accordingly, we are not persuaded by Appellants' argument.

Summary:

For the foregoing reasons, we find the totality of Appellants' arguments unpersuasive. Instead, we find that the preponderance of the evidence favors the Examiner's conclusion that a person of ordinary skill in the art would have found it prima facie obvious to have generated a dosage formulation comprising "a humanized antibody or a human monoclonal antibody as taught by Queen . . . and Engelman . . . , for use in the method disclosed by Krivan" (Answer 5-6). Further, we find that the preponderance

of the evidence favors the Examiner's conclusion that it "would have been further obvious to select antibodies against a single α or β subunit in view of Perera['s] . . . and Williams['] demonstration of neutralizing monoclonal antibodies against these specific subunits" (Answer 6).

Secondary evidence of non-obviousness:

Appellants direct our attention to several Declarations to demonstrate that:

1. "neonatal gnotobiotic colostrum deprived piglets have a unique potential as a model to evaluate prophylactic or therapeutic approaches offering new advantages to prevent or lessen systemic complications of EHEC (enterohemorrhagic *E. coli*)^[3] infection in humans" (Gunzer Declaration ¶ 5);

2. "the gnotobiotic piglet is the best model for evaluating therapies for the prevention or treatment of tissue damage by STEC infection . . ." (Leong Declaration ¶ 4); and

3. "piglets are the only model which can be used to determine the therapeutic dose against the systemic effect of the Stx" (Tzipori Declaration ¶ 4). Nevertheless, Tzipori declares that "[t]he exact injectable dose required to establish this amount of antibody in the blood stream of human individual [to be fully protected against the development of HUS] will be determined in a dose-response study during phase I clinical trials" (Tzipori Declaration ¶ 5).

³ According to Appellants' Specification "enterohemorrhagic *Escherichia coli* (EHEC), [are] now more commonly referred to as Shiga toxin producing *E. coli* (STEC). . ." (Specification 2).

We are not persuaded by this evidence. The evidence relied upon by the Examiner, which teaches the use of antibodies to treat HUS in humans, is not a new therapeutic approach to the disease. Instead, as discussed above, Krivan expressly teaches the use of antibodies to treat SLT related disease, including HUS, in humans. Accordingly, while the declaratory evidence may suggest that a pig model is useful to explore new therapeutic approaches, the evidence of record has already established that antibodies are useful in the treatment of SLT related disease in humans.

We are also not persuaded by Tzipiri's declaration that piglets are the only model that can be used to determine a therapeutic dose. Krivan discloses that

[t]he actual amount of IgG or antibodies to be administered for a prophylactic or therapeutic effect will depend upon the particular disorder being treated and the size and/or age of the human or animal. Such dosages will be readily determinable by those of ordinary skill in the art, given the teachings contained herein. The usual dose range would be 100 mg to 5 gm of immunoglobulin.

(Krivan, col. 10, ll. 48-54.) Appellants do not refute that Krivan discloses a dosage that would be considered by those of ordinary skill in the art to be an effective dosage. Instead, Appellants assert that while "[t]he dosage Krivan provides is for oral administration . . . [Krivan's dosage of] 100 mg to 5 grams, greatly exceeds the amount that would be parenterally administered a human child" (Br. 30). Not only does claim 26 not require parenteral administration, claim 26 also does not require treatment of a human child. Further, as Tzipiri declares, a person of ordinary skill in this art would recognize that the exact dosage is a results effective variable that is readily determined in dose-response studies (Tzipori Declaration ¶ 5). This is fully

supported by Krivan's teaching that "[t]he actual amount of IgG or antibodies to be administered for a prophylactic or therapeutic effect will depend upon the particular disorder being treated and the size and/or age of the human or animal" (Krivan, col. 10, ll. 48-51). For the same reasons we are not persuaded by Appellants' assertion that "[t]he art . . . fails to suggest using an appropriate animal model that would lead one of skill in the art to determine an effective dosage" (Br. 30) or that while "Williams defines a 'therapeutic amount' . . . as 'that amount of antitoxin required to neutralize the pathologic effects of *E. coli* toxin in a subject' [t]here is no indication of what this actually constitutes . . ." (Reply Br. 7).

We also recognize Tzipiri's statement that "polyclonal antibodies made in animals, however purified, cannot be injected into the blood stream of humans, either for treatment or prevention"; that Krivan provides no evidence that the antibodies are effective when orally administered; and that Krivan provides no evidence that the administration of "antibody might safely and effectively protect, ameliorate, or prevent Stx-mediated systemic disease" (Tzipiri Declaration ¶ 7). We are not persuaded by these statements for a number of reasons:

1. There is no requirement in Appellants' claim 26 that the antibody be injected into the blood stream of a human or administered orally. Appellants fail to address Krivan's teaching that pharmaceutical preparations may be administered by injection or topical application, intravenously, orally, intradermally, subcutaneously, intraocularly, subconjunctively, intramuscularly, and intrathecally (Krivan, col. 11, ll. 15-20),

2. Tzipiri fails to address the combined teachings of the references relied upon by the Examiner, which include a recognition that it would have been prima facie obvious to a person of ordinary skill in the art to produce human or humanized antibodies for the advantages taught by Queen and Engleman,

3. Tzipiri's statements fail to recognize the presumption of validity associated with the claims of an issued United States patent. *See* 35 U.S.C. 282 ("[a] patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form shall be presumed valid independently of the validity of other claims . . ."). In this regard, we direct attention to claims 17 and 18 of Krivan, which are specifically directed to the use of both a prophylactically effective amount and a therapeutically effective amount of anti-SLT antibodies in the treatment of SLT related diseases in humans.

In addition, we recognize Appellants' assertion that the claimed technology "is currently being developed using non-profit research funds due to the critical need for such a product, a need which has been known for many years but for which there is still no accepted product available to clinicians" (Br. 9). Counsel's assertion notwithstanding, there is no evidence on this record to support a finding of a long-felt need for the claimed invention. As set forth in *In re Kahn*, 441 F.3d 977, 990-91, 78 USPQ2d 1329, 1338-39 (Fed. Cir. 2006), alteration original,

our precedent requires that the applicant submit actual evidence of long-felt need, as opposed to argument. This is because "[a]bsent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004)

Absent evidence to the contrary, we are not persuaded by Appellants' asserted long-felt need for the claimed technology.

Summary:

For the foregoing reasons, we find the totality of Appellants' arguments, Declaratory evidence, and asserted long-felt need unpersuasive. Instead, for the foregoing reasons, we find that the preponderance of the evidence on this record weighs in favor of the Examiner's conclusion that claim 26 is *prima facie* obvious over the combination of Krivan, Perera, Williams, Queen and Engelman. Accordingly, we affirm the rejection of claim 26 under 35 U.S.C § 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman.

Claim 28:

Claim 28 depends from and further limits the antibody of claim 26 to those that are produced by recombinant DNA methodology. Queen teaches methodology to produce recombinant antibodies (FF 11-13).

We recognize Appellants' assertion that "[t]he prior art does not teach administration of humanized (claim 27), recombinant (claim 28) or chimeric humanized antibodies (claim 29)" (Br. 29). The prior art relied upon by the Examiner teaches administration of antibodies, and provides reasons why a person of ordinary skill in the art would seek to modify non-human antibodies to humanized, recombinant or chimeric forms. Therefore, we are not persuaded by Appellants' assertions.

Accordingly, we affirm the rejection of claim 28 under 35 U.S.C

§ 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman. Claims 27 and 29 fall together with claim 28.

Claim 30:

Claim 30 depends from and further limits the antibody of claim 26 to an antibody that binds the alpha subunit of the Shiga like toxin II. Perera teaches “five monoclonal antibodies which bind to the α -subunit of SLT-II and were able to neutralize the toxin” (FF 7).

We recognize Appellants’ assertion that “[t]he prior art does not teach administration of humanized (claim 27), recombinant (claim 28) or chimeric humanized antibodies (claim 29)” (Br. 29). The prior art relied upon by the Examiner teaches administration of antibodies, and provides reasons why a person of ordinary skill in the art would seek to modified non-human antibodies to humanized, recombinant or chimeric forms. Therefore, we are not persuaded by Appellants’ assertions.

Accordingly, we affirm the rejection of claim 30 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman. Claim 33 falls together with claim 30.

Claim 31:

Claim 31 depends from and further limits the antibodies of claim 26 to require that the antibodies are effective to prevent neurological signs of hemolytic uremic syndrome or lesions, wherein the neurological signs or lesions are selected from the group consisting of *bloody diarrhea*, acute renal failure, cerebral hemorrhaging, bacterial shedding into feces, bacterial lesions, paddling, head-pressing, ataxia, convulsions and wasting.

According to Appellants, claim 31 calls for the “alleviation of specific symptoms” (Br. 26). Krivan teaches that “[t]he host or patient is preferably a mammal and most preferably a human or a pig. The primary diseases to be targeted are *bloody diarrhea*, . . . in humans . . .” (Krivan, col. 10, ll. 43-47, emphasis added). Accordingly Krivan teaches the alleviation of one of the diseases set forth in Appellants’ claims 31.

Accordingly, we affirm the rejection of claim 31 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman.

Claim 32:

Claim 32 depends from and further limits the effective dosage of claim 26 to one that prolongs survival. As discussed above, Krivan teaches the treatment and prevention of SLT related diseases. More specifically, Krivan teaches that

the invention encompasses a pharmaceutical composition for the prevention, amelioration, or treatment of disease in a human or animal caused by SLT or by bacteria that produce an SLT. The composition comprises, in a carrier, an effective amount of the IgG or antibodies of the invention for such prevention, amelioration, or treatment.

(Krivan, col. 10, ll. 57-64.) While Appellants assert that claim 32 requires an amount that prolongs survival (Reply Br. 12), absent evidence to the contrary, to which there is none, we find that by treating or preventing SLT related disease survival is prolonged.

Accordingly, we affirm the rejection of claim 32 under 35 U.S.C.

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§ 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman. Claims 34-36 fall together with claim 32.

CONCLUSION

In summary, we affirm the rejection of claims 26-36 under 35 U.S.C. § 103(a) as unpatentable over the combination of Krivan, Perera, Williams, Queen and Engelman.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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